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=> s screening assays
L1        12394 SCREENING ASSAYS

=> s l1 and VEGF-D
L2            2 L1 AND VEGF-D

=> dup remove l2
PROCESSING COMPLETED FOR L2
L3            2 DUP REMOVE L2 (0 DUPLICATES REMOVED)

=> d l3 1-2 cbib abs

L3   ANSWER 1 OF 2     MEDLINE on STN
2004140625.     PubMed ID: 15032727.   Development of vascular endothelial
     growth factor receptor (VEGFR) kinase inhibitors as anti-angiogenic agents
     in cancer therapy. Underiner T L; Ruggeri B; Gingrich D E. (Departments of
     Chemistry and Oncolgy, Cephalon, Inc, West Chester, PA, USA..
     tunderin@cephalon.com) . Current medicinal chemistry, (2004 Mar) 11 (6)
     731-45.  Ref: 106. Journal code: 9440157. ISSN: 0929-8673. Pub. country:
     Netherlands. Language: English.
AB   Among the known angiogenic growth factors and cytokines implicated in the
     modulation of normal and pathological angiogenesis, the VEGF family
     (VEGF-A, VEGF-B, VEGF-C, VEGF-D) and their
     corresponding receptor tyrosine kinases [VEGFR-1 (Flt-1), VEGFR-2 (Flk-1,
     KDR), and VEGFR-3 (Flt-4)] play a paramount and indispensable role in
     regulating the multiple facets of the angiogenic and lymphangiogenic
     processes, as well as the induction of vascular permeability and
     inflammation. The receptor VEGFR-2/KDR is the principal one through which
     VEGFs exert their mitogenic, chemotactic, and vascular permeabilizing
     effects on the host vasculature. Increased expression of VEGFs by tumor
     cells and VEGFR-2/KDR and VEGFR-1/Flt-1 by the tumor-associated
     vasculature are a hallmark of a variety of human and rodent tumors in vivo
     and correlates with tumor growth rate, micro-vessel density/proliferation,
     tumor metastatic potential, and poorer patient prognosis in a variety of
     malignancies. Approaches to disrupting the VEGF/VEGFR signaling cascade
     range from biological agents (soluble receptors, anti-VEGF and
     anti-VEGFR-2 antibodies, and VEGF transcription inhibitors) to small
     molecule ATP competitive VEGFR inhibitors. Examples from this latter
     class that are currently in clinical development include compounds from
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distinct chemical classes such as: indolin-2-ones, anilinoquinazolines, anilinophthalazines, isothiazoles, indolo- and indenocarbazoles. The structure activity relationships, biochemical and pharmacological profile of optimized representatives from each of these classes constitute the subject matter of this review.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
2003:173752 Document No. 138:215251 **Screening assays** for identifying differentiation-inducing agents, and production of differentiated cells for cell therapy. West, Michael D.; Page, Raymond; Scholer, Hans; Chapman, Karen (Advanced Cell Technology, Inc., USA). PCT Int. Appl. WO 2003018760 A2 20030306, 100 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US26945 20020826. PRIORITY: US 2001-PV314316 20010824.
AB The invention relates to assays for screening growth factors, adhesion mols., immunostimulatory mols., extracellular matrix components and other materials, alone or in combination, simultaneously or temporally, for the ability to induce directed differentiation of pluripotent and multipotent stem cells.

=> s l1 and anti-VEGF-D
L4 0 L1 AND ANTI-VEGF-D

=> s l1 and detection
L5 1209 L1 AND DETECTION

=> s l5 and "VEGF-D"
L6 0 L5 AND "VEGF-D"

=> s anti-VEGF-D
L7 9 ANTI-VEGF-D

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PROCESSING COMPLETED FOR L7
L8 5 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 1-5 cbib abs

L8 ANSWER 1 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2002:334517 Document No.: PREV200200334517. Antibodies to truncated VEGF-D and thereof. Achen, Marc G. [Inventor, Reprint author]; Stacker, Steven Alan [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.
AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated VEGF-D. One of these antibodies can interfere with the activity of VEGF-D mediated by VEGFR-2 and interfere with the binding of VEGF-D to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L8 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2003:154373 Document No.: PREV200300154373. Expression of Vascular Endothelial Growth Factors, Vegf-B, Vegf-C, Vegf-D, and of VegfC Receptors, Flt-4

(VEGFR-3) in Inflamed and Vascularized Human Corneas. Philipp, W. E. [Reprint Author]; Speicher, L. [Reprint Author]. Department of Ophthalmology, University of Innsbruck, Innsbruck, Austria. ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 1755. cd-rom.
Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.
Language: English.

AB Purpose: Vascular endothelial growth factors are key modulators of vasculogenesis and angiogenesis. VEGF-B, VEGF-C, and VEGF-D are newly discovered growth factors that show close homology to VEGF. Since VEGF and its receptors Flt-1 and Flk-1 are strongly expressed in vascularized corneas, we investigated the expression of VEGF-B, C, D, and of VEGF-C receptor, Flt-4 (VEGFR-3), in inflamed and vascularized human corneas to help define a possible role of these cytokines in the pathogenesis of corneal neovascularization. Methods: 26 vascularized human corneas were obtained at the time of penetrating keratoplasty in patients with various inflammatory corneal diseases. Immunohistochemistry was performed on frozen sections using the streptavidin-biotin-peroxidase method and antibodies against VEGF-B, C, D, Flt-4, and against von Willebrand's factor to confirm the presence of neovascularization. Results: While only weak immunostaining for VEGF-B and VEGF-C was found on superficial corneal epithelial cells, all epithelial layers strongly stained with **anti -VEGF-D** antibody in corneas with chemical burns, herpetic stromal keratitis, atopic keratitis, zoster keratitis, fungal keratitis, and chronic allograft rejection. Flt-4 was strongly expressed on endothelial cells of limbal vessels, of newly formed vessels in the stroma, and interestingly, moderately on corneal endothelial cells. Conclusions: These results demonstrate that VEGF-D, and to a lesser extent also VEGF-B, VEGF-C, and VEGFR-3 are expressed in inflamed and vascularized human corneas and may play a role in the pathogenesis of corneal neovascularization.

L8 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2001:112744 Document No.: PREV200100112744. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Stacker, Steven A. [Reprint author]; Caesar, Carol; Baldwin, Megan E.; Thornton, Gillian E.; Williams, Richard A.; Prevo, Remko; Jackson, David G.; Nishikawa, Shin-Ichi; Kubo, Hajime; Achen, Marc G.. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, VIC, Australia.
steven.stacker@ludwig.edu.au. Nature Medicine, (February, 2001) Vol. 7, No. 2, pp. 186-191. print.
ISSN: 1078-8956. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (VEGF)-D, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that VEGF-D induced the formation of lymphatics within tumors. Moreover, expression of VEGF-D in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. VEGF-D also promoted tumor angiogenesis and growth. Lymphatic spread induced by VEGF-D could be blocked with an antibody specific for VEGF-D. This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L8 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2001:255208 Document No.: PREV200100255208. Vascular endothelial growth factor-D (VEGF-D) is an endothelial hyperpermeability inducing growth factor differentially expressed in human cardiac allografts. Wong, D. [Reprint author]; Luckhurst, J. [Reprint author]; Toma, H. [Reprint author]; Kuipers, N. [Reprint author]; Loo, S. [Reprint author]; Suarez,

A. [Reprint author]; Wilson, J. E. [Reprint author]; McManus, B. M. [Reprint author]. University of British Columbia - St. Paul's Hospital, Vancouver, BC, Canada. Journal of Heart and Lung Transplantation, (February, 2001) Vol. 20, No. 2, pp. 156. print.
Meeting Info.: Twenty-First Annual Meeting and Scientific Sessions of the International Society for Heart and Lung Transplantation. Vancouver, Canada. April 25-28, 2001. International Society for Heart and Lung Transplantation.
ISSN: 1053-2498. Language: English.

L8 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 1
2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. Achen M G; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; Stacker S A. (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.
AB Vascular endothelial growth factor-D (VEGF-D), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and lymphangiogenesis. VEGF-D consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human VEGF-D in order to generate VEGF-D antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed VEGF-D. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature VEGF-D for binding to both VEGFR-2 and VEGFR-3 for binding to mature VEGF-D. This indicates that the binding epitopes on VEGF-D for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to VEGF-D. The **anti**-(**VEGF-D**) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of VEGF-D.

=> s (achen m?/au or stacker s?/au)
L9 467 (ACHEN M?/AU OR STACKER S?/AU)

=> s l9 and VEGF antibody
L10 5 L9 AND VEGF ANTIBODY

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PROCESSING COMPLETED FOR L10
L11 1 DUP REMOVE L10 (4 DUPLICATES REMOVED)

=> d l11 cbib abs

L11 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2001156199. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. **Achen M G**; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; **Stacker S A.** (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . Journal of pathology, (2001 Feb) 193 (2) 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.
AB Expression of angiogenic and lymphangiogenic factors by tumours may

influence the route of metastatic spread. Vascular endothelial growth factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing anti-**VEGF antibodies** indicated that other angiogenic factors may be involved. VEGF-D may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 (VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal antibodies to the receptor-binding domain of VEGF-D and the use of these antibodies to localize VEGF-D in malignant melanoma. VEGF-D was detected in tumour cells and in vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which VEGF-D, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, VEGF-D was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of VEGF-D in smooth muscle of the blood vessels suggest that VEGF-D produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

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=> s l9 and "VEGF-D"
L12         138 L9 AND "VEGF-D"

=> dup remove l12
PROCESSING COMPLETED FOR L12
L13          46 DUP REMOVE L12 (92 DUPLICATES REMOVED)

=> s l13 and detection
L14           4 L13 AND DETECTION

=> dup remove l14
PROCESSING COMPLETED FOR L14
L15           4 DUP REMOVE L14 (0 DUPLICATES REMOVED)

=> d l15 1-4 cbib abs

L15  ANSWER 1 OF 4  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation  on STN
2004:265559  Document No.: PREV200400271525. Antibodies to truncated
     VEGF-D and uses thereof. Achen, Marc G.
     [Inventor, Reprint Author]; Stacker, Steven Alan [Inventor].
     Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research.
     Patent Info.: US 6730489 20040504. Official Gazette of the United States
     Patent and Trademark Office Patents, (May 4 2004) Vol. 1282, No. 1.
     http://www.uspto.gov/web/menu/patdata.html. e-file.
     ISSN: 0098-1133 (ISSN print). Language: English.
AB   The invention is based on the isolation of antibodies that were made to a
     polypeptide having the amino acid sequence for a truncated VEGF-
     D. One of these antibodies can interfere with the activity of
     VEGF-D mediated by VEGFR-2 and interfere with the
     binding of VEGF-D to VEGFR-3 but does not interfere
     with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The
     invention provides pharmaceutical and diagnostic compositions and methods
     utilizing these antibodies.

L15  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2005 ACS on STN
2002:575554  Document No. 137:135068  Methods for treating neoplastic disease
     characterized by vascular endothelial growth factor D expression, for
     screening for neoplastic disease or metastatic risk, and for maintaining
     vascularization of tissue. Achen, Marc; Stacker, Steven
     (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp.,
     Cont.-in-part of U.S. Ser. No. 796,714.  (English). CODEN: USXXCO.
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APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-PV186361 20000302; US 2000-PV234196 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of **VEGF-D** involving screening to find an organism with tumor cells expressing **VEGF-D** and administering an effective amount of a **VEGF-D** antagonist; a method for screening for neoplastic disease, where **detection** of **VEGF-D** on or in a sample such as tumor cells, blood vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism involving administering a vascularization promoting amount of **VEGF-D** or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving **detection** of **VEGF-D** on or in a tissue sample which indicates metastasis of a neoplastic disease.

L15 ANSWER 3 OF 4 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2002:407154 Document No.: PREV200200407154. The role of tumor lymphangiogenesis in metastatic spread. **Stacker, Steven A.** [Reprint author]; Baldwin, Megan E.; **Achen, Marc G.**. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Post Office Box 2008, Melbourne, VIC, 3050, Australia. steven.stacker@ludwig.edu.au. FASEB Journal, (July, 2002) Vol. 16, No. 9, pp. 922-934. print. CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

AB The high mortality rates associated with cancer can be attributed to the metastatic spread of tumor cells from the site of their origin. Tumor cells invade either the blood or lymphatic vessels to access the general circulation and then establish themselves in other tissues. Clinicopathological data suggest that the lymphatics are an initial route for the spread of solid tumors. **Detection** of sentinel lymph nodes by biopsy provides significant information for staging and designing therapeutic regimens. The role of angiogenesis in facilitating the growth of solid tumors has been well established, but the presence of lymphatic vessels and the relevance of lymphangiogenesis to tumor spread are less clear. Recently, the molecular pathway that signals for lymphangiogenesis and relatively specific markers for lymphatic endothelium have been described allowing analyses of tumor lymphangiogenesis to be performed in animal models. These studies demonstrate that tumor lymphangiogenesis is a major component of the metastatic process and implicate members of the VEGF family of growth factors as key mediators of lymphangiogenesis in both normal biology and tumors.

L15 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

2001:661270 Document No. 135:205534 Methods for treating, screening for, and detecting cancers expressing vascular endothelial growth factor D (**VEGF-D**). **Achen, Marc; Stacker, Steven** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001064235 A1 20010907, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US6791 20010302. PRIORITY: US 2000-PV186361 20000302.

AB A method for treating and alleviating melanomas and various cancers characterized by the expression of **VEGF-D** by the tumor comprises screening to find an organism with tumor cells expressing **VEGF-D** and administering an effective amount of a **VEGF-D** antagonist to prevent binding of **VEGF-**

D. Also provided are methods for screening for neoplastic diseases, where **detection** of **VEGF-D** on or in cells such as tumor cells, blood vessel endothelial cells, lymph vessel endothelial cells, and/or cells with potential neoplastic growth indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism by administering **VEGF-D** or a fragment or analog thereof; methods for screening tumors for metastatic risk where expression of **VEGF-D** by the tumor indicates metastatic risk; and methods to detect micro-metastasis of neoplastic disease where **detection** of **VEGF-D** on or in a tissue sample indicates metastasis of neoplastic disease.

=> d l13 1-46 cbib abs

L13 ANSWER 1 OF 46 MEDLINE on STN DUPLICATE 1
2005113639. PubMed ID: 15743836. Vascular endothelial growth factor D is dispensable for development of the lymphatic system. Baldwin Megan E; Halford Michael M; Roufail Sally; Williams Richard A; Hibbs Margaret L; Grail Dianne; Kubo Hajime; **Stacker Steven A**; **Achen Marc G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, PO Box 2008, Parkville, Victoria 3050, Australia.) Molecular and cellular biology, (2005 Mar) 25 (6) 2441-9. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor receptor 3 (Vegfr-3) is a tyrosine kinase that is expressed on the lymphatic endothelium and that signals for the growth of the lymphatic vessels (lymphangiogenesis). **Vegf-d**, a secreted glycoprotein, is one of two known activating ligands for Vegfr-3, the other being Vegf-c. **Vegf-d** stimulates lymphangiogenesis in tissues and tumors; however, its role in embryonic development was previously unknown. Here we report the generation and analysis of mutant mice deficient for **Vegf-d**. **Vegf-d**-deficient mice were healthy and fertile, had normal body mass, and displayed no pathologic changes consistent with a defect in lymphatic function. The lungs, sites of strong **Vegf-d** gene expression during embryogenesis in wild-type mice, were normal in **Vegf-d**-deficient mice with respect to tissue mass and morphology, except that the abundance of the lymphatics adjacent to bronchioles was slightly reduced. Dye uptake experiments indicated that large lymphatics under the skin were present in normal locations and were functional. Smaller dermal lymphatics were similar in number, location, and function to those in wild-type controls. The lack of a profound lymphatic phenotype in **Vegf-d** -deficient mice suggests that **Vegf-d** does not play a major role in lymphatic development or that Vegf-c or another, as-yet-unknown activating Vegfr-3 ligand can compensate for **Vegf-d** during development.

L13 ANSWER 2 OF 46 MEDLINE on STN DUPLICATE 2
2005290592. PubMed ID: 15759018. Gene transfer using the mature form of **VEGF-D** reduces neointimal thickening through nitric oxide-dependent mechanism. Rutanen J; Turunen A-M; Teittinen M; Rissanen T T; Heikura T; Koponen J K; Gruchala M; Inkala M; Jauhiainen S; Hiltunen M O; Turunen M P; **Stacker S A**; **Achen M G**; Yla-Herttuala S. (1Department of Molecular Medicine, A.I. Virtanen Institute, University of Kuopio, Kuopio, Finland.) Gene therapy, (2005 Jun) 12 (12) 980-7. Journal code: 9421525. ISSN: 0969-7128. Pub. country: England: United Kingdom. Language: English.

AB Gene transfer to the vessel wall using vascular endothelial growth factors (VEGFs) has shown therapeutic potential for the treatment of restenosis. In this study, we evaluated the effect of catheter-mediated adenoviral (Ad) gene transfer of the mature form of **VEGF-D** (**VEGF-D**(DeltaNDeltaC)) in balloon-denuded cholesterol-fed rabbit aorta. AdLacZ was used as a control. Transduced **VEGF-D**(DeltaNDeltaC) mRNA was detectable in the arterial wall with

RT-PCR at 6, 14 and 28 days. Gene transfer efficiency as detected with X-gal staining 6 days after the AdLacZ transduction was 1.91+/-1.32% in intima. AdVEGF-D(DeltaNDeltaC) gene transfer led to 52% reduction in intima/media ratio (I/M) as compared to the AdLacZ controls at 14 days time point. At 6 days there were no differences in I/M, but the number of macrophages in the vessel wall was 85% lower in the AdVEGF-D(DeltaNDeltaC) group as compared to the controls. The therapeutic effect was no longer detectable 28 days after the gene transfer. The therapeutic effect of **VEGF-D**(DeltaNDeltaC) was nitric oxide (NO)-dependent as the feeding of NO synthase inhibitor, L-NAME, blocked the reduction in intimal thickening. It is concluded that AdVEGF-D(DeltaNDeltaC) gene transfer reduces intimal thickening and macrophage influx into the vessel wall in balloon-denuded rabbit aortas.Gene Therapy (2005) 12, 980-987. doi:10.1038/sj.gt.3302489 Published online 10 March 2005.

L13 ANSWER 3 OF 46 MEDLINE on STN DUPLICATE 3

2005075177. PubMed ID: 15668734. Pathogenesis of persistent lymphatic vessel hyperplasia in chronic airway inflammation. Baluk Peter; Tammela Tuomas; Ator Erin; Lyubynska Natalya; **Achen Marc G**; Hicklin Daniel J; Jeltsch Michael; Petrova Tatiana V; Pytowski Bronislaw; **Stacker Steven A**; Yla-Herttuala Seppo; Jackson David G; Alitalo Kari; McDonald Donald M. (Cardiovascular Research Institute, Comprehensive Cancer Center, and Department of Anatomy, UCSF, San Francisco, California 94143, USA.) Journal of clinical investigation, (2005 Feb) 115 (2) 247-57. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Edema occurs in asthma and other inflammatory diseases when the rate of plasma leakage from blood vessels exceeds the drainage through lymphatic vessels and other routes. It is unclear to what extent lymphatic vessels grow to compensate for increased leakage during inflammation and what drives the lymphangiogenesis that does occur. We addressed these issues in mouse models of (a) chronic respiratory tract infection with Mycoplasma pulmonis and (b) adenoviral transduction of airway epithelium with VEGF family growth factors. Blood vessel remodeling and lymphangiogenesis were both robust in infected airways. Inhibition of VEGFR-3 signaling completely prevented the growth of lymphatic vessels but not blood vessels. Lack of lymphatic growth exaggerated mucosal edema and reduced the hypertrophy of draining lymph nodes. Airway dendritic cells, macrophages, neutrophils, and epithelial cells expressed the VEGFR-3 ligands VEGF-C or **VEGF-D**. Adenoviral delivery of either VEGF-C or **VEGF-D** evoked lymphangiogenesis without angiogenesis, whereas adenoviral VEGF had the opposite effect. After antibiotic treatment of the infection, inflammation and remodeling of blood vessels quickly subsided, but lymphatic vessels persisted. Together, these findings suggest that when lymphangiogenesis is impaired, airway inflammation may lead to bronchial lymphedema and exaggerated airflow obstruction. Correction of defective lymphangiogenesis may benefit the treatment of asthma and other inflammatory airway diseases.

L13 ANSWER 4 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:265559 Document No.: PREV200400271525. Antibodies to truncated **VEGF-D** and uses thereof. **Achen, Marc G.** [Inventor, Reprint Author]; **Stacker, Steven Alan** [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6730489 20040504. Official Gazette of the United States Patent and Trademark Office Patents, (May 4 2004) Vol. 1282, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated **VEGF-D**. One of these antibodies can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods

utilizing these antibodies.

L13 ANSWER 5 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:151659 Document No.: PREV200400154672. Growth factor. **Achen, Marc G.** [Inventor, Reprint Author]; Wilks, Andrew F. [Inventor]; **Stacker, Steven A.** [Inventor]; Alitalo, Kari [Inventor]. North Melbourne, Australia. ASSIGNEE: Ludwig Institute for Cancer Research; Helsinki University Licensing Ltd., Helsinki, Finland. Patent Info.: US 6689580 20040210. Official Gazette of the United States Patent and Trademark Office Patents, (Feb 10 2004) Vol. 1279, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print). Language: English.
AB **VEGF-D**, a new member of the PDGF family of growth factors, which among other things stimulates endothelial cell proliferation and angiogenesis and increases vascular permeability, as well as nucleotide sequences encoding it, methods for producing it, antibodies and other antagonists to it, transfected or transformed host cells for expressing it, pharmaceutical compositions containing it, and uses thereof in medical and diagnostic applications.

L13 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2004:80837 Document No. 140:139546 Methods and compositions for activating or inhibiting **VEGF-D** and VEGF-C. Mccoll, Bradley; Baldwin, Megan; **Stacker, Steven**; **Achen, Marc** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2004009773 A2 20040129, 30 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US22521 20030721. PRIORITY: US 2002-PV397580 20020723; US 2003-PV445234 20030206; US 2003-PV485741 20030710.
AB Methods for activating endothelial growth factors VEGF-C or **VEGF-D** with plasmin, and methods of treatment comprising administering a pharmaceutical compns. comprising plasmin. Also disclosed are methods of screening for inhibitors of activation of the growth factors by plasmin, and method of treatment by blocking activation of VEGF-C/D activation by plasmin. Further disclosed are methods for screening for other proteases that activate VEGF-CD, and for inhibitors of such activation. The invention further includes inhibitors of plasmin activity and methods of treating patients in need thereof with said inhibitors.

L13 ANSWER 7 OF 46 MEDLINE on STN DUPLICATE 4
2004393015. PubMed ID: 15297417. Expression of vascular endothelial growth factor receptor-3 by lymphatic endothelial cells is associated with lymph node metastasis in prostate cancer. Zeng Yiping; Opeskin Kenneth; Baldwin Megan E; Horvath Lisa G; **Achen Marc G**; **Stacker Steven A**; Sutherland Robert L; Williams Elizabeth D. (Bernard O'Brien Institute of Microsurgery, Melbourne, Australia.) Clinical cancer research : an official journal of the American Association for Cancer Research, (2004 Aug 1) 10 (15) 5137-44. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.
AB PURPOSE: The molecular mechanisms underlying lymph node metastasis are poorly understood, despite the well-established clinical importance of lymph node status in many human cancers. Recently, vascular endothelial growth factor (VEGF)-C and **VEGF-D** have been implicated in the regulation of tumor lymphangiogenesis and enhancement of lymphatic invasion via activation of VEGF receptor-3. The purpose of this study was to determine the expression pattern of the VEGF-C/**VEGF-D**/VEGF receptor-3 axis in prostate cancer and its relationship with lymph

node metastasis. EXPERIMENTAL DESIGN: The expression pattern of VEGF-C, **VEGF-D**, and VEGF receptor-3 in localized prostate cancer specimens (n = 37) was determined using immunohistochemistry. RESULTS: Widespread, heterogeneous staining for VEGF-C and **VEGF-D** was observed in all cancer specimens. Intensity of VEGF-C staining was lower in benign prostate epithelium than in adjacent carcinoma, whereas no difference between benign epithelium and carcinoma was observed for **VEGF-D** staining. VEGF receptor-3 immunostaining was detected in endothelial cells of lymphatic vessels in 18 of 37 tissue samples. The presence of VEGF receptor-3-positive vessels was associated with lymph node metastasis (P = 0.0002), Gleason grade (P < 0.0001), extracapsular extension (P = 0.0382), and surgical margin status (P = 0.0069). In addition, VEGF receptor-3 staining highlighted lymphatic invasion by VEGF-C-positive/**VEGF-D**-positive carcinoma cells. CONCLUSIONS: Together, these results suggest that paracrine activation of lymphatic endothelial cell VEGF receptor-3 by VEGF-C and/or **VEGF-D** may be involved in lymphatic metastasis. Thus the VEGF-C/**VEGF-D**/VEGF receptor-3 signaling pathway may provide a target for antilymphangiogenic therapy in prostate cancer.

L13 ANSWER 8 OF 46 MEDLINE on STN DUPLICATE 5
2004103278. PubMed ID: 14967735. Adenoviral catheter-mediated intramyocardial gene transfer using the mature form of vascular endothelial growth factor-D induces transmural angiogenesis in porcine heart. Rutanen Juha; Rissanen Tuomas T; Markkanen Johanna E; Gruchala Marcin; Silvennoinen Paivi; Kivela Antti; Hedman Antti; Hedman Marja; Heikura Tommi; Orden Maija-Riitta; **Stacker Steven A**; **Achen Marc G**; Hartikainen Juha; Yla-Herttuala Seppo. (Department of Molecular Medicine, A.I. Virtanen Institute, Kuopio University, Finland.) Circulation, (2004 Mar 2) 109 (8) 1029-35. Electronic Publication: 2004-02-16. Journal code: 0147763. ISSN: 1524-4539. Pub. country: United States. Language: English.

AB BACKGROUND: It is unclear what is the most efficient vector and growth factor for induction of therapeutic vascular growth in the heart. Furthermore, the histological nature of angiogenesis and potential side effects caused by different vascular endothelial growth factors (VEGFs) in myocardium have not been documented. METHODS AND RESULTS: Adenoviruses (Ad) at 2 doses (2x10(11) and 2x10(12) viral particles) or naked plasmids (1 mg) encoding LacZ control, VEGF-A165, or the mature, soluble form of **VEGF-D** (**VEGF-D**(DeltaNDeltaC)) were injected intramyocardially with the NOGA catheter system into domestic pigs. AdVEGF-D(DeltaNDeltaC) gene transfer (GT) induced a dose-dependent myocardial protein production, as measured by ELISA, resulting in an efficient angiogenic effect 6 days after the injections. Also, AdVEGF-A165 produced high gene transfer efficacy, as demonstrated with immunohistochemistry, leading to prominent angiogenesis effects. Despite the catheter-mediated approach, angiogenesis induced by both AdVEGFs was transmural, with maximal effects in the epicardium. Histologically, strongly enlarged alpha-smooth muscle actin-positive microvessels involving abundant cell proliferation were found in the transduced regions, whereas microvessel density did not change. Myocardial contrast echocardiography and microspheres showed marked increases in perfusion in the transduced areas. **VEGF-D**(DeltaNDeltaC) but not matrix-bound VEGF-A165 was detected in plasma after adenoviral GT. A modified Miles assay demonstrated myocardial edema resulting in pericardial effusion with the higher AdVEGF doses. All effects returned to baseline by 3 weeks. Naked plasmid-mediated GT did not induce detectable protein production or vascular effects. CONCLUSIONS: Like AdVEGF-A165, AdVEGF-D(DeltaNDeltaC) GT using the NOGA system produces efficient transmural angiogenesis and increases myocardial perfusion. AdVEGF-D(DeltaNDeltaC) could be useful for the induction of therapeutic vascular growth in the heart.

L13 ANSWER 9 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
2004:178863 Document No.: PREV200400171899. Adenoviral catheter-mediated

intramyocardial gene transfer using the mature form of vascular endothelial growth factor-D induces transmural angiogenesis in porcine heart. Rutanen, Juha; Rissanen, Tuomas T.; Markkanen, Johanna E.; Gruchala, Marcin; Silvennoinen, Paivi; Kivela, Antti; Hedman, Antti; Hedman, Marja; Heikura, Tommi; Orden, Maija-Riitta; **Stacker, Steven A.**; **Achen, Marc G.**; Hartikainen, Juha; Yla-Herttuala, Seppo [Reprint Author]. A. I. Virtanen Institute, Kuopio University, FIN-70211, PO Box 1627, Kuopio, Finland. seppo.ylaherttuala@uku.fi. Circulation, (March 2 2004) Vol. 109, No. 3, pp. 1029-1035. print.
ISSN: 0009-7322 (ISSN print). Language: English.

AB Background: It is unclear what is the most efficient vector and growth factor for induction of therapeutic vascular growth in the heart. Furthermore, the histological nature of angiogenesis and potential side effects caused by different vascular endothelial growth factors (VEGFs) in myocardium have not been documented. Methods and Results: Adenoviruses (Ad) at 2 doses (2X1011 and 2X1012 viral particles) or naked plasmids (1 mg) encoding LacZ control, VEGF-A165, or the mature, soluble form of **VEGF-D** (VEGF-DDELTANDELTAC) were injected intramyocardially with the NOGA catheter system into domestic pigs. AdVEGF-DDELTANDELTAC gene transfer (GT) induced a dose-dependent myocardial protein production, as measured by ELISA, resulting in an efficient angiogenic effect 6 days after the injections. Also, AdVEGF-A165 produced high gene transfer efficacy, as demonstrated with immunohistochemistry, leading to prominent angiogenesis effects. Despite the catheter-mediated approach, angiogenesis induced by both AdVEGFs was transmural, with maximal effects in the epicardium. Histologically, strongly enlarged alpha-smooth muscle actin-positive microvessels involving abundant cell proliferation were found in the transduced regions, whereas microvessel density did not change. Myocardial contrast echocardiography and microspheres showed marked increases in perfusion in the transduced areas. VEGF-DDELTANDELTAC but not matrix-bound VEGF-A165 was detected in plasma after adenoviral GT. A modified Miles assay demonstrated myocardial edema resulting in pericardial effusion with the higher AdVEGF doses. All effects returned to baseline by 3 weeks. Naked plasmid-mediated GT did not induce detectable protein production or vascular effects. Conclusions: Like AdVEGF-A165, AdVEGF-DDELTANDELTAC GT using the NOGA system produces efficient transmural angiogenesis and increases myocardial perfusion. AdVEGF-DDELTANDELTAC could be useful for the induction of therapeutic vascular growth in the heart.

L13 ANSWER 10 OF 46 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2005:1756 The Genuine Article (R) Number: 878JL. Molecular regulation of the VEGF family - inducers of angiogenesis and lymphangiogenesis. McColl B K (Reprint); **Stacker S A**; **Achen M G.** Royal Melbourne Hosp, Ludwig Inst Canc Res, POB 2008, Melbourne, Vic 3050, Australia (Reprint); Royal Melbourne Hosp, Ludwig Inst Canc Res, Melbourne, Vic 3050, Australia. APMIS (JUL-AUG 2004) Vol. 112, No. 7-8, pp. 463-480. Publisher: BLACKWELL MUNKSGAARD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0903-4641. Pub. country: Australia. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The vascular endothelial growth factor (VEGF) family of secreted glycoproteins are critical inducers of angiogenesis (growth of blood vessels) and lymphangiogenesis (growth of lymphatic vessels). These proteins are attractive therapeutic targets for blocking growth of blood vessels and lymphatics in tumors and thereby inhibiting the growth and spread of cancer - in fact, the first VEGF inhibitor has recently entered the clinic for treatment of cancer. In addition, the VEGFs are being considered for stimulation of angiogenesis in the context of ischemic disease and lymphangiogenesis for treatment of lymphedema. These therapeutic possibilities have focused great interest on the molecular regulation of VEGF family members. Much has been learned in the past five years about the mechanisms controlling the action of the VEGFs, including the importance of hypoxia, proteolysis, transcription factors and RNA

splicing. An understanding of these mechanisms offers broader opportunities to manipulate expression and activity of the VEGFs for treatment of disease.

L13 ANSWER 11 OF 46 MEDLINE on STN DUPLICATE 6
2004053395. PubMed ID: 14754406. Molecular targeting of lymphatics for therapy. **Stacker S A**; Hughes R A; **Achen M G**. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Steven.stacker@ludwig.edu.au) . Current pharmaceutical design, (2004) 10 (1) 65-74. Ref: 124. Journal code: 9602487. ISSN: 1381-6128. Pub. country: Netherlands. Language: English.

AB The dysfunction or proliferation of lymphatic vessels (lymphangiogenesis) is linked to a number of pathological conditions including lymphedema and cancer. The recent discovery and characterisation of the lymphangiogenic growth factors vascular endothelial growth factor-C (VEGF-C) and **VEGF-D** and of their receptor on lymphatic endothelial cells, VEGFR-3, has provided an understanding of the molecular mechanisms controlling the growth of lymphatic vessels. In addition, other genes and protein markers have been identified with specificity for lymphatic endothelium that have enhanced the characterization and isolation of lymphatic endothelial cells. Our growing understanding of the molecules that control lymphangiogenesis allows us to design more specific drugs with which to manipulate the relevant signalling pathways. Modulating these pathways and other molecules with specificity to the lymphatic system could offer alternative treatments for a number of important clinical conditions.

L13 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2003:892882 Document No. 139:359245 Methods for the administration of **VEGF-D** DNA for the treatment and prevention of secondary lymphedema. Heinzerling, Lucie Margarete; Baldwin, Megan Elizabeth; **Stacker, Steven Alan**; **Achen, Marc Gregory** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2003093419 A2 20031113, 19 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US13350 20030429. PRIORITY: US 2002-PV377253 20020503.

AB Methods of preventing secondary lymphedema with DNA encoding **VEGF -D** and/or **VEGF-D** protein, and biol. active fragments and analogs thereof, as well as pharmaceutical compns. for treating secondary lymphedema, are presented.

L13 ANSWER 13 OF 46 MEDLINE on STN DUPLICATE 7
2003501181. PubMed ID: 14577925. Angiogenic responses of vascular endothelial growth factors in periadventitial tissue. Bhardwaj Shalini; Roy Himadri; Gruchala Marcin; Viita Helena; Kholova Ivana; Kokina Ilze; **Achen Marc G**; **Stacker Steven A**; Hedman Marja; Alitalo Kari; Yla-Herttuala Seppo. (Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Kuopio, 70211 Kuopio, Finland.) Human gene therapy, (2003 Oct 10) 14 (15) 1451-62. Journal code: 9008950. ISSN: 1043-0342. Pub. country: United States. Language: English.

AB Recent discovery of new members of the vascular endothelial growth factor (VEGF) family has generated much interest as to which members may be best suited for therapeutic angiogenesis in various tissues. In this study we evaluated angiogenic responses of the different members of the VEGF family in vivo using adenoviral gene transfer. Adenoviruses (1 x 10(9) plaque-forming units [pfu]) encoding for VEGF-A, VEGF-B, VEGF-C, **VEGF-D**, VEGF-C(deltaNdeltaC) and **VEGF-**

D(deltaNdeltaC) (deltaNdeltaC are proteolytically cleaved forms) were transferred locally to the periadventitial space of the rabbit carotid arteries using a collar technique that allows efficient local transfection of the periadventitial tissue. Expression of the transfected VEGFs was confirmed by immunohistochemistry and reverse transcription-polymerase chain reaction (RT-PCR). Seven days after the gene transfer maximum neovessel formation was observed in VEGF-A-, **VEGF-D**-, and **VEGF-D** (deltaNdeltaC)-transfected arteries. VEGF-C(deltaNdeltaC) also showed angiogenic activity whereas VEGF-B was not effective in inducing angiogenesis. Pericytes were detected around the neovessels, which also frequently showed the presence of intraluminal erythrocytes. Infiltration of inflammatory cells in response to **VEGF-D** and **VEGF-D**(deltaNdeltaC) was less prominent than that caused by other VEGFs. In line with the absence of lymphatics in the normal carotid arteries no significant evidence of lymphatic vessel formation was seen in response to any of the studied VEGFs in the periadventitial space. The results help to define possibilities for local angiogenic therapy around blood vessels and support the concept that angiogenic effects may be tissue-specific and depend both on the growth factor ligands and the target tissues. It is concluded that VEGF-A, **VEGF-D**, and **VEGF-D**(deltaNdeltaC) are the best candidates for therapeutic angiogenesis when delivered around large arteries.

L13 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2003:801321 Document No. 141:82808 Plasmin activates the lymphangiogenic growth factors VEGF-C and **VEGF-D.** [Erratum to document cited in CA140:013416]. McColl, Bradley K.; Baldwin, Megan E.; Roufail, Saly; Freeman, Craig; Moritz, Robert L.; Simpson, Richard J.; Alitalo, Kari; **Stacker, Steven A.**; **Achen, Marc G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, 3050, Australia). Journal of Experimental Medicine, 198(7), 1127 (English) 2003. CODEN: JEMEAV. ISSN: 0022-1007. Publisher: Rockefeller University Press.

AB In the Results section, subheading Assay for **VEGF-D** Processing, "kD" was used instead of the unit "D", implying that the value being quoted was 1000-fold greater than in reality. The corrected paragraph is given.

L13 ANSWER 15 OF 46 MEDLINE on STN DUPLICATE 8
2003251849. PubMed ID: 12714562. **VEGF-D** is the strongest angiogenic and lymphangiogenic effector among VEGFs delivered into skeletal muscle via adenoviruses. Rissanen Tuomas T; Markkanen Johanna E; Gruchala Marcin; Heikura Tommi; Puranen Antti; Kettunen Mikko I; Kholova Ivana; Kauppinen Risto A; **Achen Marc G**; **Stacker Steven A**; Alitalo Kari; Yla-Herttuala Seppo. (Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland.) Circulation research, (2003 May 30) 92 (10) 1098-106. Electronic Publication: 2003-04-24. Journal code: 0047103. ISSN: 1524-4571. Pub. country: United States. Language: English.

AB Optimal angiogenic and lymphangiogenic gene therapy requires knowledge of the best growth factors for each purpose. We studied the therapeutic potential of human vascular endothelial growth factor (VEGF) family members VEGF-A, VEGF-B, VEGF-C, and **VEGF-D** as well as a VEGFR-3-specific mutant (VEGF-C156S) using adenoviral gene transfer in rabbit hindlimb skeletal muscle. The significance of proteolytic processing of **VEGF-D** was explored using adenoviruses encoding either full-length or mature (DeltaNDeltaC) **VEGF-D.** Adenoviruses expressing potent VEGFR-2 ligands, VEGF-A and VEGF-DDeltaNDeltaC, induced the strongest angiogenesis and vascular permeability effects as assessed by capillary vessel and perfusion measurements, modified Miles assay, and MRI. The most significant feature of angiogenesis induced by both VEGF-A and VEGF-DDeltaNDeltaC was a remarkable enlargement of microvessels with efficient recruitment of

pericytes suggesting formation of arterioles or venules. VEGF-A also moderately increased capillary density and created glomeruloid bodies, clusters of tortuous vessels, whereas VEGF-DDeltaNDeltaC-induced angiogenesis was more diffuse. Vascular smooth muscle cell proliferation occurred in regions with increased plasma protein extravasation, indicating that arteriogenesis may be promoted by VEGF-A and VEGF-DDeltaNDeltaC. Full-length VEGF-C and **VEGF-D** induced predominantly and the selective VEGFR-3 ligand VEGF-C156S exclusively lymphangiogenesis. Unlike angiogenesis, lymphangiogenesis was not dependent on nitric oxide. The VEGFR-1 ligand VEGF-B did not promote either angiogenesis or lymphangiogenesis. Finally, we found a positive correlation between capillary size and vascular permeability. This study compares, for the first time, angiogenesis and lymphangiogenesis induced by gene transfer of different human VEGFs, and shows that **VEGF-D** is the most potent member when delivered via an adenoviral vector into skeletal muscle.

L13 ANSWER 16 OF 46 MEDLINE on STN DUPLICATE 9

2003477107. PubMed ID: 14553837. Vascular endothelial growth factor-D expression in human atherosclerotic lesions. Rutanen Juha; Leppanen Pia; Tuomisto Tiina T; Rissanen Tuomas T; Hiltunen Mikko O; Vajanto Ismo; Niemi Mari; Hakkinen Tomi; Karkola Kari; **Stacker Steven A**; **Achen Marc G**; Alitalo Kari; Yla-Herttuala Seppo. (Department of Molecular Medicine, AI Virtanen Institute, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland.) Cardiovascular research, (2003 Oct 1) 59 (4) 971-9. Journal code: 0077427. ISSN: 0008-6363. Pub. country: Netherlands. Language: English.

AB OBJECTIVE: Vascular endothelial growth factor-D (**VEGF-D**) is a recently characterized member of the VEGF family, but its expression in atherosclerotic lesions remains unknown. We studied the expression of **VEGF-D** and its receptors (VEGFR-2 and VEGFR-3) in normal and atherosclerotic human arteries, and compared that to the expression pattern of VEGF-A. METHODS: Human arterial samples (n=39) obtained from amputation operations and fast autopsies were classified according to the stage of atherosclerosis and studied by immunohistochemistry. The results were confirmed by in situ hybridization and RT-PCR. RESULTS: We found that while VEGF-A expression increased during atherogenesis, **VEGF-D** expression remained relatively stable only decreasing in complicated lesions. In normal arteries and in early lesions **VEGF-D** was mainly expressed in smooth muscle cells, whereas in complicated atherosclerotic lesions the expression was most prominent in macrophages and also colocalized with plaque neovascularization. By comparing the staining profiles of different antibodies, we found that proteolytic processing of **VEGF-D** was efficient in the vessel wall. VEGFR-2, but not VEGFR-3, was expressed in the vessel wall at every stage of atherosclerosis. CONCLUSIONS: Our results suggest that in large arteries **VEGF-D** is mainly expressed in smooth muscle cells and that it may have a role in the maintenance of vascular homeostasis. However, in complicated lesions it was also expressed in macrophages and may contribute to plaque neovascularization. The constitutive expression of VEGFR-2 in arteries suggests that it may be one of the principal mediators of the **VEGF-D** effects in large arteries.

L13 ANSWER 17 OF 46 MEDLINE on STN DUPLICATE 10

2003434367. PubMed ID: 12963694. Plasmin activates the lymphangiogenic growth factors VEGF-C and **VEGF-D**. McColl Bradley K; Baldwin Megan E; Roufail Sally; Freeman Craig; Moritz Robert L; Simpson Richard J; Alitalo Kari; **Stacker Steven A**; **Achen Marc G** . (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Melbourne, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . Journal of experimental medicine, (2003 Sep 15) 198 (6) 863-8. Electronic Publication: 2003-09-08. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor (VEGF) C and **VEGF-D**

stimulate lymphangiogenesis and angiogenesis in tissues and tumors by activating the endothelial cell surface receptor tyrosine kinases VEGF receptor (VEGFR) 2 and VEGFR-3. These growth factors are secreted as full-length inactive forms consisting of NH2- and COOH-terminal propeptides and a central VEGF homology domain (VHD) containing receptor binding sites. Proteolytic cleavage removes the propeptides to generate mature forms, consisting of dimers of the VEGF homology domain, that bind receptors with much greater affinity than the full-length forms. Therefore, proteolytic processing activates VEGF-C and **VEGF-D**, although the proteases involved were unknown. Here, we report that the serine protease plasmin cleaved both propeptides from the VEGF homology domain of human **VEGF-D** and thereby generated a mature form exhibiting greatly enhanced binding and cross-linking of VEGFR-2 and VEGFR-3 in comparison to full-length material. Plasmin also activated VEGF-C. As lymphangiogenic growth factors promote the metastatic spread of cancer via the lymphatics, the proteolytic activation of these molecules represents a potential target for antimetastatic agents. Identification of an enzyme that activates the lymphangiogenic growth factors will facilitate development of inhibitors of metastasis.

L13 ANSWER 18 OF 46 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

2004:30088 The Genuine Article (R) Number: 749NH. **VEGF-D**: A molecular regulator of lymphangiogenesis. McColl B (Reprint); Baldwin M; Roufail S; Freeman C; Moritz R; Simpson R; Alitalo K; **Stacker S ; Achen M G.** Ludwig Inst Canc Res, Helsinki, Finland; John Curtin Sch Med Res, Canberra, ACT, Australia; Biomedicum Helsinki, Canc Biol Lab, Helsinki, Finland. ATHEROSCLEROSIS SUPPLEMENTS (SEP 2003) Vol. 4, No. 2, pp. 90-90. Publisher: ELSEVIER SCI IRELAND LTD. CUSTOMER RELATIONS MANAGER, BAY 15, SHANNON INDUSTRIAL ESTATE CO, CLARE, IRELAND. ISSN: 1567-5688. Pub. country: Finland; Australia. Language: English.

L13 ANSWER 19 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2002:334517 Document No.: PREV200200334517. Antibodies to truncated **VEGF-D** and thereof. **Achen, Marc G.** [Inventor, Reprint author]; **Stacker, Steven Alan** [Inventor]. Parkville, Australia. ASSIGNEE: Ludwig Institute for Cancer Research. Patent Info.: US 6383484 20020507. Official Gazette of the United States Patent and Trademark Office Patents, (May 7, 2002) Vol. 1258, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated **VEGF-D.** One of these antibodies can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The invention provides pharmaceutical and diagnostic compositions and methods utilizing these antibodies.

L13 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN

2002:575554 Document No. 137:135068 Methods for treating neoplastic disease characterized by vascular endothelial growth factor D expression, for screening for neoplastic disease or metastatic risk, and for maintaining vascularization of tissue. **Achen, Marc; Stacker, Steven** (Australia). U.S. Pat. Appl. Publ. US 2002102260 A1 20020801, 45 pp., Cont.-in-part of U.S. Ser. No. 796,714. (English). CODEN: USXXCO. APPLICATION: US 2001-956095 20010920. PRIORITY: US 2000-PV186361 20000302; US 2000-PV234196 20000920; US 2001-796714 20010302.

AB A method for treating and alleviating disease characterized by the expression of **VEGF-D** involving screening to find an organism with tumor cells expressing **VEGF-D** and administering an effective amount of a **VEGF-D** antagonist; a method for screening for neoplastic disease, where detection

of **VEGF-D** on or in a sample such as tumor cells, blood vessel endothelial cells or lymph vessel endothelial cells indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism involving administering a vascularization promoting amount of **VEGF-D** or a fragment or analog thereof to the organism; a method for screening tumors for metastatic risk involving detecting expression of VEFG-D by a tumor which indicates metastatic risk; and a method of detecting micro-metastasis of neoplastic disease involving detection of **VEGF-D** on or in a tissue sample which indicates metastasis of a neoplastic disease.

L13 ANSWER 21 OF 46 MEDLINE on STN DUPLICATE 11

2002296322. PubMed ID: 12036873. Adenovirus encoding vascular endothelial growth factor-D induces tissue-specific vascular patterns in vivo. Byzova Tatiana V; Goldman Corey K; Jankau Jurek; Chen Juhua; Cabrera Gustavo; **Achen Marc G; Stacker Steven A**; Carnevale Kevin A; Siemionow Maria; Deitcher Steven R; DiCorleto Paul E. (Department of Molecular Cardiology and Cardiology, The Cleveland Clinic Foundation, OH 44195, USA.. byzovat@ccf.org) . Blood, (2002 Jun 15) 99 (12) 4434-42. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB The capacity of an adenovirus encoding the mature form of vascular endothelial growth factor (**VEGF**)-D, **VEGF-D** Delta N Delta C, to induce angiogenesis, lymphangiogenesis, or both was analyzed in 2 distinct in vivo models. We first demonstrated in vitro that **VEGF-D** Delta N Delta C encoded by the adenovirus (Ad-**VEGF-D** Delta N Delta C) is capable of inducing endothelial cell proliferation and migration and that the latter response is primarily mediated by VEGF receptor-2 (VEGFR-2). Second, we characterized a new in vivo model for assessing experimental angiogenesis, the rat cremaster muscle, which permits live videomicroscopy and quantitation of functional blood vessels. In this model, a proangiogenic effect of Ad-**VEGF-D** Delta N Delta C was evident as early as 5 days after injection. Immunohistochemical analysis of the cremaster muscle demonstrated that neovascularization induced by Ad-**VEGF-D** Delta N Delta C and by Ad-VEGF-A(165) (an adenovirus encoding the 165 isoform of VEGF-A) was composed primarily of laminin and VEGFR-2-positive vessels containing red blood cells, thus indicating a predominantly angiogenic response. In a skin model, Ad-**VEGF-D** Delta N Delta C induced angiogenesis and lymphangiogenesis, as indicated by staining with laminin, VEGFR-2, and VEGFR-3, whereas Ad-VEGF-A(165) stimulated the selective growth of blood vessels. These data suggest that the biologic effects of **VEGF-D** are tissue-specific and dependent on the abundance of blood vessels and lymphatics expressing the receptors for **VEGF-D** in a given tissue. The capacity of Ad-**VEGF-D** Delta N Delta C to induce endothelial cell proliferation, angiogenesis, and lymphangiogenesis demonstrates that its potential usefulness for the treatment of coronary artery disease, cerebral ischemia, peripheral vascular disease, restenosis, and tissue edema should be tested in preclinical models.

L13 ANSWER 22 OF 46 MEDLINE on STN DUPLICATE 12

2002628291. PubMed ID: 12386934. Molecular control of lymphangiogenesis. Baldwin Megan E; **Stacker Steven A; Achen Marc G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.) BioEssays : news and reviews in molecular, cellular and developmental biology, (2002 Nov) 24 (11) 1030-40. Ref: 94. Journal code: 8510851. ISSN: 0265-9247. Pub. country: England: United Kingdom. Language: English.

AB The lymphatic vasculature plays a critical role in the regulation of body fluid volume and immune function. Extensive research into the molecular mechanisms that control blood vessel growth has led to identification of molecules that also regulate development and growth of the lymphatic vessels. This is generating a great deal of interest in the molecular

control of the lymphatics in the context of embryogenesis, lymphatic disorders and tumor metastasis. Studies in animal models carried out over the past three years have shown that the soluble protein growth factors, vascular endothelial growth factor (VEGF)-C and **VEGF-D**, and their cognate receptor tyrosine kinase, VEGF receptor-3 (VEGFR-3), are critical regulators of lymphangiogenesis. Furthermore, disfunction of VEGFR-3 has recently been shown to cause lymphedema. The capacity to induce lymphangiogenesis by manipulation of the VEGF-C/**VEGF-D**/VEGFR-3 signaling pathway offers new opportunities to understand the function of the lymphatic system and to develop novel treatments for lymphatic disorders.

L13 ANSWER 23 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN DUPLICATE 13

2002:407154 Document No.: PREV200200407154. The role of tumor lymphangiogenesis in metastatic spread. **Stacker, Steven A.** [Reprint author]; Baldwin, Megan E.; **Achen, Marc G.**. Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Post Office Box 2008, Melbourne, VIC, 3050, Australia. steven.stacker@ludwig.edu.au. FASEB Journal, (July, 2002) Vol. 16, No. 9, pp. 922-934. print.
CODEN: FAJOEC. ISSN: 0892-6638. Language: English.

AB The high mortality rates associated with cancer can be attributed to the metastatic spread of tumor cells from the site of their origin. Tumor cells invade either the blood or lymphatic vessels to access the general circulation and then establish themselves in other tissues. Clinicopathological data suggest that the lymphatics are an initial route for the spread of solid tumors. Detection of sentinel lymph nodes by biopsy provides significant information for staging and designing therapeutic regimens. The role of angiogenesis in facilitating the growth of solid tumors has been well established, but the presence of lymphatic vessels and the relevance of lymphangiogenesis to tumor spread are less clear. Recently, the molecular pathway that signals for lymphangiogenesis and relatively specific markers for lymphatic endothelium have been described allowing analyses of tumor lymphangiogenesis to be performed in animal models. These studies demonstrate that tumor lymphangiogenesis is a major component of the metastatic process and implicate members of the VEGF family of growth factors as key mediators of lymphangiogenesis in both normal biology and tumors.

L13 ANSWER 24 OF 46 MEDLINE on STN DUPLICATE 14

2002399706. PubMed ID: 12148568. The angiogenic and lymphangiogenic factor vascular endothelial growth factor-D exhibits a paracrine mode of action in cancer. **Achen Marc G**; Williams Richard A; Baldwin Megan E; Lai Patricia; Roufail Sally; Alitalo Kari; **Stacker Steven A.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. Marc.achen@ludwig.edu.au) . Growth factors (Chur, Switzerland), (2002 Jun) 20 (2) 99-107. Journal code: 9000468. ISSN: 0897-7194. Pub. country: Switzerland. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**) promotes angiogenesis, lymphangiogenesis and metastatic spread via the lymphatics, however, the mode of **VEGF-D** action (e.g. paracrine vs. autocrine) was unknown. We analyzed **VEGF-D** action in human tumors and a mouse model of metastasis. **VEGF-D** was localized in tumor cells and endothelium in human non-small cell lung carcinoma and breast ductal carcinoma in situ. Tumor vessels positive for **VEGF-D** were also positive for its receptors, VEGF receptor-2 (VEGFR-2) and/or VEGFR-3 but negative for **VEGF-D** mRNA, indicating that **VEGF-D** is secreted by tumor cells and subsequently associates with endothelium via receptor-mediated uptake. The mature form of **VEGF-D** was detected in tumors demonstrating that **VEGF-D** is proteolytically processed and bioactive. In a mouse model of metastasis, **VEGF-D** synthesized in tumor cells became localized on the endothelium and thereby promoted metastatic spread. These data

indicate that **VEGF-D** promotes tumor angiogenesis, lymphangiogenesis and metastatic spread by a paracrine mechanism.

L13 ANSWER 25 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2003:80142 Document No.: PREV200300080142. Combination gene therapy for inhibition of edema induced by therapeutic angiogenesis. Markkanen, Johanna E. [Reprint Author]; Rissanen, Tuomas T. [Reprint Author]; Gruchala, Marcin [Reprint Author]; Puranen, Antti [Reprint Author]; Kettunen, Mikko I. [Reprint Author]; Kauppinen, Risto A. [Reprint Author]; **Achen, Marc G.**; **Stacker, Steven A.**; Yla-Herttuala, Seppo [Reprint Author]. A I V Institute, Kuopio, Finland. Circulation, (November 5 2002) Vol. 106, No. 19 Supplement, pp. II-238. print.
Meeting Info.: Abstracts from Scientific Sessions. Chicago, IL, USA. November 17-20, 2002. American Heart Association.
ISSN: 0009-7322 (ISSN print). Language: English.

L13 ANSWER 26 OF 46 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

2001:534079 Document No.: PREV200100534079. Vascular endothelial growth factor-D (**VEGF-D**) polypeptides. **Achen, Marc G.** [Inventor, Reprint author]; Wilks, Andrew F. [Inventor]; **Stacker, Steven A.** [Inventor]; Alitalo, Kari [Inventor]. Fitzroy, Australia. ASSIGNEE: Ludwig Institute for Cancer Research; Helsinki University Licensing Ltd., Helsinki, Finland. Patent Info.: US 6235713 20010522. Official Gazette of the United States Patent and Trademark Office Patents, (May 22, 2001) Vol. 1246, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133. Language: English.

AB **VEGF-D**, a new member of the PDGF family of growth factors, which among other things stimulates endothelial cell proliferation and angiogenesis and increases vascular permeability, as well as nucleotide sequences encoding it, methods for producing it, antibodies and other antagonists to it, transfected or transformed host cells for expressing it, pharmaceutical compositions containing it, and uses thereof in medical and diagnostic applications.

L13 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN

2001:661270 Document No. 135:205534 Methods for treating, screening for, and detecting cancers expressing vascular endothelial growth factor D (**VEGF-D**). **Achen, Marc**; **Stacker, Steven** (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001064235 A1 20010907, 78 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.
APPLICATION: WO 2001-US6791 20010302. PRIORITY: US 2000-PV186361 20000302.

AB A method for treating and alleviating melanomas and various cancers characterized by the expression of **VEGF-D** by the tumor comprises screening to find an organism with tumor cells expressing **VEGF-D** and administering an effective amount of a **VEGF-D** antagonist to prevent binding of **VEGF-D**. Also provided are methods for screening for neoplastic diseases, where detection of **VEGF-D** on or in cells such as tumor cells, blood vessel endothelial cells, lymph vessel endothelial cells, and/or cells with potential neoplastic growth indicates neoplastic disease; a method for promoting and maintaining vascularization of normal tissue in an organism by administering **VEGF-D** or a fragment or analog thereof; methods for screening tumors for metastatic risk where expression of **VEGF-D** by the tumor indicates metastatic risk; and methods to detect micro-metastasis of

neoplastic disease where detection of **VEGF-D** on or in a tissue sample indicates metastasis of neoplastic disease.

L13 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of VEGF, VEGF-C, and **VEGF-D**, preparation methods, pharmaceutical compositions, and therapeutic use. **Achen, Marc G.** ; Hughes, Richard A.; **Stacker, Steven**; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides monomeric monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of **VEGF-D** , as well as methods of making them, pharmaceutical compns. containing them, and therapeutic methods of use.

L13 ANSWER 29 OF 46 MEDLINE on STN DUPLICATE 15
2001679531. PubMed ID: 11574540. Multiple forms of mouse vascular endothelial growth factor-D are generated by RNA splicing and proteolysis. Baldwin M E; Roufail S; Halford M M; Alitalo K; **Stacker S A**; **Achen M G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Post Office Box 2008, Victoria 3050, Australia.) Journal of biological chemistry, (2001 Nov 23) 276 (47) 44307-14. Electronic Publication: 2001-09-26. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The secreted glycoprotein vascular endothelial growth factor-D (**VEGF-D**) is angiogenic, lymphangiogenic, and promotes metastatic spread of tumor cells via lymphatic vessels. **VEGF-D** consists of a receptor-binding domain (VEGF homology domain) and N- and C-terminal propeptides. Proteolytic processing produces numerous forms of human **VEGF-D**, including fully processed derivatives (containing only the VEGF homology domain), partially processed, and unprocessed derivatives. Proteolysis is essential to generate human **VEGF-D** that binds the angiogenic receptor VEGF receptor-2 (VEGFR-2) and the lymphangiogenic receptor VEGFR-3 with high affinity. Here, we report that alternative use of an RNA splice donor site in exon 6 of the mouse **VEGF-D** gene produces two different protein isoforms, **VEGF-D** (358) and **VEGF-D**(326), with distinct C termini. The two isoforms were both expressed in all adult mouse tissues and embryonic stages of development analyzed. Both isoforms are proteolytically processed in a similar fashion to human **VEGF-D** to generate a range of secreted derivatives and bind and cross-link VEGFR-3 with similar potency. The isoforms are differently glycosylated when expressed in vitro. This study demonstrates that RNA splicing, protein glycosylation, and proteolysis are mechanisms for generating structural diversity of mouse **VEGF-D.**

L13 ANSWER 30 OF 46 MEDLINE on STN DUPLICATE 16
2001328395. PubMed ID: 11279005. The specificity of receptor binding by vascular endothelial growth factor-d is different in mouse and man. Baldwin M E; Catimel B; Nice E C; Roufail S; Hall N E; Stenvers K L; Karkkainen M J; Alitalo K; **Stacker S A**; **Achen M G.** (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050 Australia.) Journal of biological chemistry, (2001 Jun 1) 276 (22) 19166-71. Electronic Publication:

2001-02-20. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Human vascular endothelial growth factor-D (**VEGF-D**) binds and activates VEGFR-2 and VEGFR-3, receptors expressed on vascular and lymphatic endothelial cells. As VEGFR-2 signals for angiogenesis and VEGFR-3 is thought to signal for lymphangiogenesis, it was proposed that **VEGF-D** stimulates growth of blood vessels and lymphatic vessels into regions of embryos and tumors. Here we report the unexpected finding that mouse **VEGF-D** fails to bind mouse VEGFR-2 but binds and cross-links VEGFR-3 as demonstrated by biosensor analysis with immobilized receptor domains and bioassays of VEGFR-2 and VEGFR-3 cross-linking. Mutation of amino acids in mouse **VEGF-D** to those in the human homologue indicated that residues important for the VEGFR-2 interaction are clustered at, or are near, the predicted receptor-binding surface. Coordinated expression of **VEGF-D** and VEGFR-3 in mouse embryos was detected in the developing skin where the **VEGF-D** gene was expressed in a layer of cells beneath the developing epidermis and VEGFR-3 was localized on a network of vessels immediately beneath the **VEGF-D**-positive cells. This suggests that **VEGF-D** and VEGFR-3 may play a role in establishing vessels of the skin by a paracrine mechanism. Our study of receptor specificity suggests that **VEGF-D** may have different biological functions in mouse and man.

L13 ANSWER 31 OF 46 MEDLINE on STN DUPLICATE 17

2001509463. PubMed ID: 11532940. Isolated lymphatic endothelial cells transduce growth, survival and migratory signals via the VEGF-C/D receptor VEGFR-3. Makinen T; Veikkola T; Mustjoki S; Karpanen T; Catimel B; Nice E C; Wise L; Mercer A; Kowalski H; Kerjaschki D; **Stacker S A**; **Achen M G**; Alitalo K. (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, and Helsinki University Hospital, Biomedicum Helsinki, University of Helsinki, FIN-00014 Helsinki, Finland.) EMBO journal, (2001 Sep 3) 20 (17) 4762-73. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3/Flt4) binds two known members of the VEGF ligand family, VEGF-C and **VEGF-D**, and has a critical function in the remodelling of the primary capillary vasculature of midgestation embryos. Later during development, VEGFR-3 regulates the growth and maintenance of the lymphatic vessels. In the present study, we have isolated and cultured stable lineages of blood vascular and lymphatic endothelial cells from human primary microvascular endothelium by using antibodies against the extracellular domain of VEGFR-3. We show that VEGFR-3 stimulation alone protects the lymphatic endothelial cells from serum deprivation-induced apoptosis and induces their growth and migration. At least some of these signals are transduced via a protein kinase C-dependent activation of the p42/p44 MAPK signalling cascade and via a wortmannin-sensitive induction of Akt phosphorylation. These results define the critical role of VEGF-C/VEGFR-3 signalling in the growth and survival of lymphatic endothelial cells. The culture of isolated lymphatic endothelial cells should now allow further studies of the molecular properties of these cells.

L13 ANSWER 32 OF 46 MEDLINE on STN DUPLICATE 18

2001216875. PubMed ID: 11250889. Signalling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. Veikkola T; Jussila L; Makinen T; Karpanen T; Jeltsch M; Petrova T V; Kubo H; Thurston G; McDonald D M; **Achen M G**; **Stacker S A**; Alitalo K. (Molecular/Cancer Biology Laboratory and Ludwig Institute for Cancer Research, Haartman Institute, University of Helsinki, PO Box 21 (Haartmaninkatu 3), 00014 Helsinki, Finland.) EMBO journal, (2001 Mar 15) 20 (6) 1223-31. Journal code: 8208664. ISSN: 0261-4189. Pub. country: England: United Kingdom. Language: English.

AB Vascular endothelial growth factor receptor-3 (VEGFR-3) has an essential role in the development of embryonic blood vessels; however, after midgestation its expression becomes restricted mainly to the developing

lymphatic vessels. The VEGFR-3 ligand VEGF-C stimulates lymphangiogenesis in transgenic mice and in chick chorioallantoic membrane. As VEGF-C also binds VEGFR-2, which is expressed in lymphatic endothelia, it is not clear which receptors are responsible for the lymphangiogenic effects of VEGF-C. **VEGF-D**, which binds to the same receptors, has been reported to induce angiogenesis, but its lymphangiogenic potential is not known. In order to define the lymphangiogenic signalling pathway we have created transgenic mice overexpressing a VEGFR-3-specific mutant of VEGF-C (VEGF-C156S) or **VEGF-D** in epidermal keratinocytes under the keratin 14 promoter. Both transgenes induced the growth of lymphatic vessels in the skin, whereas the blood vessel architecture was not affected. Evidence was also obtained that these growth factors act in a paracrine manner in vivo. These results demonstrate that stimulation of the VEGFR-3 signal transduction pathway is sufficient to induce specifically lymphangiogenesis in vivo.

L13 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2003:439275 Document No. 139:83053 **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; **Achen, Marc G.**; **Stacker, Steven A.**; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.
AB On the cover, "mutliforme" should be "multiforme".

L13 ANSWER 34 OF 46 MEDLINE on STN DUPLICATE 19
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; **Achen M G**; **Stacker S A**; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.
AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer

therapies.

L13 ANSWER 35 OF 46 MEDLINE on STN DUPLICATE 20
2001212643. PubMed ID: 11175849. **VEGF-D** promotes the metastatic spread of tumor cells via the lymphatics. **Stacker S A** ; Caesar C; Baldwin M E; Thornton G E; Williams R A; Prevo R; Jackson D G; Nishikawa S; Kubo H; **Achen M G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.) Nature medicine, (2001 Feb) 7 (2) 186-91. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Metastasis to local lymph nodes via the lymphatic vessels is a common step in the spread of solid tumors. To investigate the molecular mechanisms underlying the spread of cancer by the lymphatics, we examined the ability of vascular endothelial growth factor (**VEGF**)-**D**, a ligand for the lymphatic growth factor receptor VEGFR-3/Flt-4, to induce formation of lymphatics in a mouse tumor model. Staining with markers specific for lymphatic endothelium demonstrated that **VEGF**-**D** induced the formation of lymphatics within tumors. Moreover, expression of **VEGF-D** in tumor cells led to spread of the tumor to lymph nodes, whereas expression of VEGF, an angiogenic growth factor which activates VEGFR-2 but not VEGFR-3, did not. **VEGF**-**D** also promoted tumor angiogenesis and growth. Lymphatic spread induced by **VEGF-D** could be blocked with an antibody specific for **VEGF-D.** This study demonstrates that lymphatics can be established in solid tumors and implicates VEGF family members in determining the route of metastatic spread.

L13 ANSWER 36 OF 46 MEDLINE on STN DUPLICATE 21
2001156199. PubMed ID: 11180159. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumour angiogenesis. **Achen M G**; Williams R A; Minekus M P; Thornton G E; Stenvers K; Rogers P A; Lederman F; Roufail S; **Stacker S A.** (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050, Australia.. Marc.achen@ludwig.edu.au) . Journal of pathology, (2001 Feb) 193 (2) 147-54. Journal code: 0204634. ISSN: 0022-3417. Pub. country: England: United Kingdom. Language: English.

AB Expression of angiogenic and lymphangiogenic factors by tumours may influence the route of metastatic spread. Vascular endothelial growth factor (VEGF) is a regulator of tumour angiogenesis, but studies of the inhibition of solid tumour growth by neutralizing anti-VEGF antibodies indicated that other angiogenic factors may be involved. **VEGF**-**D** may be an alternative regulator because like VEGF it is angiogenic and it activates VEGF receptor-2 (VEGFR-2), an endothelial cell receptor which is a key signalling molecule in tumour angiogenesis. This study reports the generation of monoclonal antibodies to the receptor-binding domain of **VEGF-D** and the use of these antibodies to localize **VEGF-D** in malignant melanoma. **VEGF-D** was detected in tumour cells and in vessels adjacent to immunopositive tumour cells, but not in vessels distant from the tumours. These findings are consistent with a model in which **VEGF-D**, secreted by tumour cells, activates endothelial cell receptors and thereby contributes to the regulation of tumour angiogenesis and possibly lymphangiogenesis. In addition, **VEGF**-**D** was detected in the vascular smooth muscle, but not the endothelium, of vessels in adult colon. The endothelium of these vessels was negative for VEGFR-2 and VEGFR-3. As VEGF receptors can be up-regulated on endothelium in response to vessel damage and ischaemia, these findings of a specific localization of **VEGF-D** in smooth muscle of the blood vessels suggest that **VEGF-D** produced by vascular smooth muscle could play a role in vascular repair by stimulating the proliferation of endothelial cells.

L13 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
2000:441581 Document No. 133:72945 Antibodies to truncated **VEGF**-**D** and uses thereof. **Achen, Marc G.; Stacker,**

Steven Alan (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2000037025 A2 20000629, 44 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US31332 19991221. PRIORITY: US 1998-PV113254 19981221; US 1999-PV134556 19990517.

AB The invention is based on the isolation of antibodies that were made to a polypeptide having the amino acid sequence for a truncated **VEGF-D**. One of these antibodies can interfere with the activity of **VEGF-D** mediated by VEGFR-2 and interfere with the binding of **VEGF-D** to VEGFR-3 but does not interfere with the activity of VEGF mediated by VEGFR-2 or bind to VEGF-C. The antibodies, antibody fragments or compns. containing the antibodies are useful for diagnosis, prognosis, and therapy of **VEGF-D** or VEGF-C related diseases, e.g. cancer, diabetic retinopathy, psoriasis, arthropathy, fluid accumulation in the heart and/or lung.

L13 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN

2000:290851 Document No. 132:318341 Use of VEGF-C or **VEGF-D** gene or protein to prevent restenosis. Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.; Jeltsch, Markku M.; **Achen, Marc G.** (Ludwig Institute for Cancer Research, USA; Helsinki University Licensing Ltd. Oy). PCT Int. Appl. WO 2000024412 A2 20000504, 61 pp. DESIGNATED STATES: W: AU, CA, CN, JP, NO, NZ; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US24054 19991026. PRIORITY: US 1998-PV105587 19981026.

AB The present invention provides materials and methods for preventing stenosis or restenosis of a blood vessel using Vascular Endothelial Growth Factor C (VEGF-C) and/or Vascular Endothelial Growth Factor D (**VEGF-D**) genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a composition effective to prevent restenosis, said composition comprising at least one anti-restenosis agent selected from the group consisting of a VEGF-C polynucleotide, a VEGF-C polypeptide, a **VEGF-D** polynucleotide, and a **VEGF-D** polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating restenosis comprising a container holding at least one anti-restenosis agent of the invention and a label attached to or packaged with the container, the label describing use of the compound for prevention of restenosis of a blood vessel. The kit further comprises a medical device of the invention.

L13 ANSWER 39 OF 46 MEDLINE on STN DUPLICATE 22

2000247148. PubMed ID: 10785369. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. **Achen M G**; Roufail S; Domagala T; Catimel B; Nice E C; Geleick D M; Murphy R; Scott A M; Caesar C; Makinen T; Alitalo K; **Stacker S A.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. marc.achen@ludwig.edu.au) . European journal of biochemistry / FEBS, (2000 May) 267 (9) 2505-15. Journal code: 0107600. ISSN: 0014-2956. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**), the most recently discovered mammalian member of the VEGF family, is an angiogenic protein that activates VEGF receptor-2 (VEGFR-2/Flk1/KDR) and VEGFR-3 (Flt4). These receptor tyrosine kinases, localized on vascular and lymphatic endothelial cells, signal for angiogenesis and

lymphangiogenesis. **VEGF-D** consists of a central receptor-binding VEGF homology domain (VHD) and N-terminal and C-terminal propeptides that are cleaved from the VHD to generate a mature, bioactive form consisting of dimers of the VHD. Here we report characterization of mAbs raised to the VHD of human **VEGF-D** in order to generate **VEGF-D** antagonists. The mAbs bind the fully processed VHD with high affinity and also bind unprocessed **VEGF-D**. We demonstrate, using bioassays for the binding and cross-linking of VEGFR-2 and VEGFR-3 and biosensor analysis with immobilized receptors, that one of the mAbs, designated VD1, is able to compete potently with mature **VEGF-D** for binding to both VEGFR-2 and VEGFR-3 for binding to mature **VEGF-D**. This indicates that the binding epitopes on **VEGF-D** for these two receptors may be in close proximity. Furthermore, VD1 blocks the mitogenic response of human microvascular endothelial cells to **VEGF-D**. The anti-(**VEGF-D**) mAbs raised to the bioactive region of this growth factor will be powerful tools for analysis of the biological functions of **VEGF-D**

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L13 ANSWER 40 OF 46 MEDLINE on STN DUPLICATE 23

2001021068. PubMed ID: 11023993. VEGF-C and **VEGF-D** expression in neuroendocrine cells and their receptor, VEGFR-3, in fenestrated blood vessels in human tissues. Partanen T A; Arola J; Saaristo A; Jussila L; Ora A; Miettinen M; **Stacker S A**; **Achen M G**; Alitalo K. (Molecular/Cancer Biology Laboratory and Department of Pathology, Haartman Institute, University of Helsinki, 00014 Helsinki, Finland.) FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2000 Oct) 14 (13) 2087-96. Journal code: 8804484. ISSN: 0892-6638. Pub. country: United States. Language: English.

AB Recently, vascular endothelial growth factor receptor 3 (VEGFR-3) has been shown to provide a specific marker for lymphatic endothelia in certain human tissues. In this study, we have investigated the expression of VEGFR-3 and its ligands VEGF-C and **VEGF-D** in fetal and adult tissues. VEGFR-3 was consistently detected in the endothelium of lymphatic vessels such as the thoracic duct, but fenestrated capillaries of several organs including the bone marrow, splenic and hepatic sinusoids, kidney glomeruli and endocrine glands also expressed this receptor. VEGF-C and **VEGF-D**, which bind both VEGFR-2 and VEGFR-3 were expressed in vascular smooth muscle cells. In addition, intense cytoplasmic staining for VEGF-C was observed in neuroendocrine cells such as the alpha cells of the islets of Langerhans, prolactin secreting cells of the anterior pituitary, adrenal medullary cells, and dispersed neuroendocrine cells of the gastrointestinal tract. **VEGF-D** was observed in the innermost zone of the adrenal cortex and in certain dispersed neuroendocrine cells. These results suggest that VEGF-C and **VEGF-D** have a paracrine function and perhaps a role in peptide release from secretory granules of certain neuroendocrine cells to surrounding capillaries.

L13 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN

2000:773478 Document No. 134:66223 Growth factors regulating lymphatic vessels. Lymboussaki, A.; **Achen, M. G.**; **Stacker, S. A.** ; Alitalo, K. (Molecular/Cancer Biology Laboratory, Haartman Institute, University of Helsinki, Finland, 00014, Finland). Current Topics in Microbiology and Immunology, 251(Lymphoid Organogenesis), 75-82 (English) 2000. CODEN: CTMIA3. ISSN: 0070-217X. Publisher: Springer-Verlag.

AB A review with 44 refs. Over the past 10 yr, much has been learned about the mol. control of angiogenesis, but only recently have the first regulators of lymphangiogenesis been identified. The availability of VEGF-C and **VEGF-D** offers the opportunity to induce lymphangiogenesis in the clinic, which may be useful for treatment of lymphedema. The expression of VEGF-C and **VEGF-D** in tumors raises the possibility of tumor lymphangiogenesis. Despite

involvement of the lymphatics in tumor metastasis, little is known about the relationship between tumor cells and the lymphatic endothelium. The route by which a tumor metastasizes may, in part, be determined by the angiogenic/lymphangiogenic growth factors secreted by tumor cells that modulate the prevalence of vessels in a tumor. Specific inhibitors of VEGF-C, **VEGF-D** or VEGFR-3 will be required to address this important issue.

L13 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
1999:468435 Document No. 131:83470 Expression vectors and cell lines expressing vascular endothelial growth factor D, and method of treating melanomas. **Achen, Marc G.**; **Stacker, Steven Alan**; Alitalo, Kari (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 9933485 A1 19990708, 79 pp. DESIGNATED STATES: W: AU, CA, CN, JP, KR, NZ; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US27373 19981223. PRIORITY: AU 1997-1131 19971224; US 1998-87392 19980529.
AB This invention relates to expression vectors comprising **VEGF-D** and its biol. active derivs., cell lines stably expressing **VEGF-D** and its biol. active derivs., and to a method of making a polypeptide using these expression vectors and host cells. Optionally, **VEGF-D** produced by the cell line of the invention is linked to an epitope tag such as FLAG, hexahistidine, or I-SPY, to facilitate purification of the polypeptide by affinity chromatog. The mammalian cell line may preferably be the 293-EBNA human embryonal kidney cell line, and several Apex-3 plasmid expression constructs are provided. The invention also relates to a method for treating and alleviating melanomas or tumors expressing **VEGF-D** and various diseases.

L13 ANSWER 43 OF 46 MEDLINE on STN DUPLICATE 24
2000044745. PubMed ID: 10574962. A mutant form of vascular endothelial growth factor (VEGF) that lacks VEGF receptor-2 activation retains the ability to induce vascular permeability. **Stacker S A**; Vitali A; Caesar C; Domagala T; Groenen L C; Nice E; **Achen M G**; Wilks A F. (Ludwig Institute for Cancer Research, Post Office Box 2008, Royal Melbourne Hospital, Victoria 3050 Australia.. Steven.stacker@ludwig.edu.au) . Journal of biological chemistry, (1999 Dec 3) 274 (49) 34884-92. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB Vascular endothelial growth factor (VEGF) is a major mediator of vasculogenesis and angiogenesis both during development and in pathological conditions. VEGF has a variety of effects on vascular endothelium, including the ability to stimulate endothelial cell mitogenesis, and the potent induction of vascular permeability. These activities are at least in part mediated by binding to two high affinity receptors, VEGFR-1 and VEGFR-2. In this study we have made mutations of mouse VEGF in order to define the regions that are required for VEGFR-2-mediated functions. Development of a bioassay, which responds only to signals generated by cross-linking of VEGFR-2, has allowed evaluation of these mutants for their ability to activate VEGFR-2. One mutant (VEGF0), which had amino acids 83-89 of VEGF substituted with the analogous region of the related placenta growth factor, demonstrated significantly reduced VEGFR-2 binding compared with wild type VEGF, indicating that this region was required for VEGF-VEGFR-2 interaction. Intriguingly, when this mutant was evaluated in a Miles assay for its ability to induce vascular permeability, no difference was found when compared with wild type VEGF. In addition we have shown that the VEGF homology domain of the structurally related growth factor **VEGF-D** is capable of binding to and activating VEGFR-2 but has no vascular permeability activity, indicating that VEGFR-2 binding does not correlate with permeability activity for all VEGF family members. These data suggest different mechanisms for VEGF-mediated mitogenesis and vascular permeability and raise the possibility of an alternative receptor mediating vascular permeability.

L13 ANSWER 44 OF 46 MEDLINE on STN DUPLICATE 25
2000011413. PubMed ID: 10542248. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. **Stacker S A**; Stenvers K; Caesar C; Vitali A; Domagala T; Nice E; Roufail S; Simpson R J; Moritz R; Karpanen T; Alitalo K; **Achen M G.** (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia.. steven.stacker@ludwig.edu.au) . Journal of biological chemistry, (1999 Nov 5) 274 (45) 32127-36. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Vascular endothelial growth factor-D (**VEGF-D**) binds and activates the endothelial cell tyrosine kinase receptors VEGF receptor-2 (VEGFR-2) and VEGF receptor-3 (VEGFR-3), is mitogenic for endothelial cells, and shares structural homology and receptor specificity with VEGF-C. The primary translation product of **VEGF-D** has long N- and C-terminal polypeptide extensions in addition to a central VEGF homology domain (VHD). The VHD of **VEGF-D** is sufficient to bind and activate VEGFR-2 and VEGFR-3. Here we report that **VEGF-D** is proteolytically processed to release the VHD. Studies in 293EBNA cells demonstrated that **VEGF-D** undergoes N- and C-terminal cleavage events to produce numerous secreted polypeptides including a fully processed form of M(r) approximately 21,000 consisting only of the VHD, which is predominantly a non-covalent dimer. Biosensor analysis demonstrated that the VHD has approximately 290- and approximately 40-fold greater affinity for VEGFR-2 and VEGFR-3, respectively, compared with unprocessed **VEGF-D.** In situ hybridization demonstrated that embryonic lung is a major site of expression of the **VEGF-D** gene. Processed forms of **VEGF-D** were detected in embryonic lung indicating that **VEGF-D** is proteolytically processed in vivo.

L13 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2005 ACS on STN
1998:151220 Document No. 128:213742 Vascular endothelial cell growth factor D (**VEGF-D**) and a cDNA encoding and their uses.
Achen, Marc G.; Wilks, Andrew F.; **Stacker, Steven A.**; Alitalo, Kari (Ludwig Institute for Cancer Research, USA; Helsinki University Licensing Ltd., Oy). PCT Int. Appl. WO 9807832 A1 19980226, 101 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US14696 19970821. PRIORITY: AU 1996-1825 19960823; US 1996-23751 19960823; AU 1996-3554 19961111; US 1996-31097 19961114; AU 1997-4954 19970205; US 1997-38814 19970210; AU 1997-7435 19970619; US 1997-51426 19970701.

AB **VEGF-D**, a new member of the PDGF family of growth factors, which among other things stimulates endothelial cell proliferation and angiogenesis and increases vascular permeability, is described. A cDNA encoding it is cloned. Methods for manufacture of **VEGF-D**, antibodies and other antagonists to it, transgenic cells for manufacture of the protein, pharmaceutical compns. containing it, and its therapeutic and diagnostic uses are also described. An EST clone encoding a novel member of the VEGF family was identified during a database search. This partial sequence was used to probe a human breast cDNA library and a full-length clone obtained. The protein shows amino acid sequence similarities to VEGF-C and to Tie-2 ligand 1. A bioassay was used to demonstrate that **VEGF-D** bound the gene KDR receptor and stimulated endothelial cell proliferation.

L13 ANSWER 46 OF 46 MEDLINE on STN DUPLICATE 26

1998118549. PubMed ID: 9435229. Vascular endothelial growth factor D (**VEGF-D**) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4). **Achen M G**; Jeltsch M; Kukk E; Makinen T; Vitali A; Wilks A F; Alitalo K; **Stacker S A** . (Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia.. Marc.achen@ludwig.edu.au) . Proceedings of the National Academy of Sciences of the United States of America, (1998 Jan 20) 95 (2) 548-53. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We have identified a member of the VEGF family by computer-based homology searching and have designated it **VEGF-D. VEGF -D** is most closely related to VEGF-C by virtue of the presence of N- and C-terminal extensions that are not found in other VEGF family members. In adult human tissues, **VEGF-D** mRNA is most abundant in heart, lung, skeletal muscle, colon, and small intestine. Analyses of **VEGF-D** receptor specificity revealed that **VEGF-D** is a ligand for both VEGF receptors (VEGFRs) VEGFR-2 (Flk1) and VEGFR-3 (Flt4) and can activate these receptors. However. **VEGF-D** does not bind to VEGFR-1. Expression of a truncated derivative of **VEGF-D** demonstrated that the receptor-binding capacities reside in the portion of the molecule that is most closely related in primary structure to other VEGF family members and that corresponds to the mature form of VEGF-C. In addition, **VEGF-D** is a mitogen for endothelial cells. The structural and functional similarities between **VEGF-D** and VEGF-C define a subfamily of the VEGFs.

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